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Novel approaches to enhance oral bioavailability of poorly soluble drugs

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ABSTRACT

Oral administration is considered as major, convenient route among all other routes of delivery, owing to several benefits. But, the poor solubility or enzymatic/metabolic activity are the major concerns in developing a successful formulation. About 40% of approved drugs which are in the current market and 90% of new drug molecules in the developmental pipeline are hydrophobic in nature. The challenge to formulate insoluble drugs has met with various approaches to overcome the problems related to solubility, application of nanotechnology is one amongst them. The present review deals with various nanocarriers and technologies that are proven to be effective in enhancing the bioavilability of poorly soluble drugs.

Keywords: Lipids; Polymers; Oral Bioavailability; Nanoparticles; Nanoemulsions, Nanofibers.

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INTRODUCTION

Oral drug delivery is considered as most suitable, common and broadly used as it offers many advantages in the vein of patient compliance and cost in contrast to other routes such as mucosal, transdermal and pulmonary [1]. Nevertheless, numerous compounds are ineffective and fails in research and development process owing to their low solubility, thus minimising the absorption and bioavailability [2-3]. As estimated, nearly 40% of approved drugs and 90% of molecules in the development stages are suffering with the solubility issues. Some of the reasons for this are as follows; i) Unavailability of drug in solution form, ii) first pass metabolism, iii) inadequate partition coefficient, iv) degradation of drug in gastro intestinal tract and v) p-glycoprotein mediated efflux (which can alter the pharmacokinetics) [4]. Quite a few approaches have been applied to enhance the oral absorption and bioavailability of hydrophobic drugs such as, hydrotrophy, micronization and solid dispersions. Since few years, nanocarriers are attain incredible attention and have shown notable advantages over conventional systems, especially for low soluble drugs [5].

Traditional methodologies in enhancing the solubility

Several conventional methods like Co-solvency and surfactant solubilisation; pH modification, microparticles [6,7] and salt forms; Cyclodextrins (CDs); solid state modification including, amorphous forms, solid dispersions and co-crystals etc. CDs (Inclusion complexation) are the are the multipurpose excipients studied widely for pharmaceutical purposes. Solid dispersion is one of the technology that is explored broadly in the recent decades specially for the delivery of low soluble drugs [8]. Localization of conventional dosage forms can also results in enhancing the bioavailability as evident from several studies on coating [9], mucoadhesion [10,11], and floating approaches [12]. Fast dissolving tablets and matrix dosage forms are also established their application in enhancing the absorption [13,14].

Novel technologies in delivery of poorly soluble drugs

The most frequent nanotechnology based strategies used in the formulation development are solid lipid nanoparticles, polymeric nanoparticles, dendrimers, liposomes, micelles, carobon nanotubes and so forth [Figure 1]. which an further provide controlled or

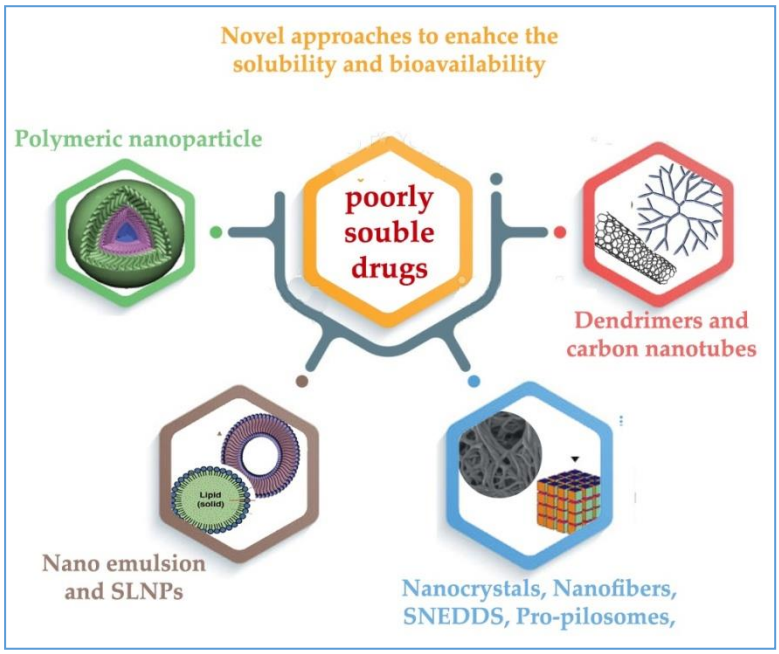

Figure 1: Some of the novel approaches to enhance the solubility and bioavailability of poorly soluble drugs

sustained or targeted drug delivery. At this time, all these novel systems are explored effectively in enhancing the therapeutic efficacy especially in anti-cancer, anti-diabetic and non-steroidal anti-inflammatory drugs etc.

Polymeric nanoparticles are the colloidal carriers having particle size in the range of 10-100 nm. Application of polymeric nanoparticles can enhance the bioavailability, specificity and reduce toxicity. These nanoparticles can be prepared by using several natural and synthetic polymers [15-19]. These carriers were successfully employed for gene delivery and tumor targeting. The therapeutic efficacy is significantly depends on biodegradation of polymer and drug release, usually the drug release follows erosion mechanism, diffusion mechanism of combination of both [20].

Solid Lipid nanoparticles (SLN) are the sub-micron colloidal carriers, which were composed of physiological lipids, which are dispersed in aqueous or aqueous surfactant solution. SLNs can offer other benefits such as non-toxicity, biocompatibility and stability, that can be applied for the delivery of hydrophobic as well as hydrophillic drugs [21].

Nanoemulsions are O/W type on emulsions having the droplet size of 100-500 nm and can provide advantages like solubilization of poorly soluble drugs in the oil phase and modifies the oil droplet with polymers to prolong the circulation time and also to target several tumors passively or actively (by adding ligands) [22]. Commonly used methods are double emulsion, low and high energy emulsification etc. SNEDDS (Self nano emulsifying drug delivery systems) are anhydrous hydrotrophic mixture of surfactant, oil and drug, subsequently added to the aqueous phase with continuous stirring to form the SNEDDS. Apart from the benefits of nanoemulsions, SNEDDS can further enhances the chemical, enzymatic stability of drug molecule, and ease of scale up and fabrication [23].

Nanocrystals are having the atoms size in the range of 10-400 nm, prepared from nanosuspension consisting of the following steps. i) preparation of nanosuspension, ii) wet milling, iii) high pressure homogenization iv) nanocrystallization and v) spray drying [24,25]. Mallesh Kurakula et al., have investigated the efficacy of nanocrystals in enhancing the solubility and dissolution rate of Atorvastatin [26].

Proliposomes are dry, free flowing powder with a dispersed system, which can immediately form a liposomal suspension on contact with water. Owing to their solid properties, proliposomes can enhance the physical stability and promote drug absorption [27-31].

Dendrimers are the novel innovative polymeric carrier having three dimensional structure, narrow polydispersity index, controlled molecular structure and accompanied with several multiple functional groups. Dendrimers having the size in between 1 to 100 nm with three distinct domains i) core, containing a molecule or atom, ii) repeated branches and iii) terminal functional groups. Currently, carbon nanotubes are gaining remarkable attention as novel carriers owing to their unique features such as a) higher cellular uptake, ii) enhanced transmembrane penetration and iii) high drug loading [32]. Apart from all these novel systems, nanowires, nanofibers, nanoethanosomes and nanofilms are gained their importance in enhancing the oral bioavailability of poorly soluble drugs [33-38]. Though the optimizing of several parameters in preparing optimum nano-formulation is bit complicated, several applications like quality by design/ response surface methodology or PAT can be successfully applied [39-44].

CONCLUSION

Application of nanotechnology holds a great potential in the effective delivery of several poorly soluble drugs. All the foresaid technologies are appeared as various strategies to revitalize the current development process. The colloidal size, low dose size reduced toxicity and patient compliance are the main benefits, adding a special note to drug targeting. Several research works were revealed this. Even though the several significant achievements are made in nano field, yet there are few challenges that have been encountered, like a) scale up, b) variation of pharmacokinetics among the individuals and c) cost and d) reproducibility. Thus, nanotechnology can offers several opportunities for the researchers to extend their research and development to overcome the foresaid challenges.

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